Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Oath/Declaration

The Examiner stated that the oath or declaration is defective because "it does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration." Applicants have submitted a new declaration in compliance with 37 CFR 1.67(a) identifying the present application by number and filing date and claiming priority under 35 USC §119(e) to U.S. provisional application no. 60/104,589 filed February 7, 1997 and under 35 USC §120 to U.S. application number 08/938,830, filed September 29, 1997 and PCT application 98/01774 filed January 30, 1998.

Applicants believe that the new declaration is in compliance with 37 CFR 1.67(a) and respectfully request its consideration by the Examiner.

Specification

The Examiner objected to the specification on several grounds. First, the Examiner stated that "this application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b)." Applicants respectfully submit that an abstract on a separate sheet was submitted as page 88 of the application. A replacement sheet has been attached to the present Response as it was inadvertently not included with the response mailed on November 7, 2000. The replacement sheet is a copy of page 88 as originally filed and contains no new matter.

In addition, the Examiner stated that the specification must be amended to reflect the priority claimed in the Declaration. Applicants have amended the specification to reflect the priority claimed in the accompanying substitute Declaration.

Sequence Listing

As indicated on the attached Notice to Comply with the Sequence Rules or CRF Diskette Problem Report, the diskette provided by Applicants was not acceptable. In addition, as a result of the amendment to the priority claim, the priority application information in the Substitute Sequence Listing submitted by Applicants on January 23, 2001 is incorrect. The accompanying new sequence listing reflects the amendment to the priority claim and provides a new CRF diskette. The new Sequence Listing does not include new matter and the computer readable form, submitted in accordance with 37 C.F.R. § 1.825(b), is the same as the paper form of the Sequence Listing.

Claim Rejections Under 35 U.S.C. §101

Applicants are pleased to note the withdrawal of the claim rejections under 35 U.S.C. §101.

Claim Rejections Under 35 U.S.C. §112

The rejection of Claims 15 through 18 and 22 under 35 U.S.C. §112, first paragraph has been maintained. This rejection would now also be applicable to new claim 23. The Examiner states that although the §101 utility rejection has been withdrawn "the standard used by the Office in determining whether the specification is enabling is different, requiring that the invention, as drawn to the full scope of the claims, be supported by either a specific and substantial or a well-established asserted utility." As the Examiner has recognized, "the utility of the claimed antibody depends upon the utility of the polypeptide to which it binds." The Examiner's arguments are thus directed to the utility of the PSTPIP-polypeptides, and the Examiner concludes that "because one cannot predict whether a PSPIP-like polypeptide variant will have the ability to induce actin polymerization or that it will be expressed in a cell cycle-dependent manner, and therefore an antibody capable of specifically binding to the variant is not supported by a specific asserted utility, one skilled in the art clearly would not know how to use the claimed invention drawn to the full breadth of the claims."

Applicants believe that the Examiner's position directly contradicts the view already taken by the Patent Office. The claims in the present application cover the same scope of

variants as those covered by the issued claims in U.S. Patent No. 6,111,073 for PSTPIP polypeptides. Thus, the Patent Office has already made a determination that one skilled in the art would know how to make and use the claimed PSTPIP variant polypeptides based on an identical disclosure. As the utility of the claimed antibodies follows from the utility of the PSTPIP polypeptides, Applicants submit that this rejection should be withdrawn.

Additionally, the Examiner has maintained the rejection of claim 22 stating that from the claim language it is implicit that a candidate agonist or antagonist antibody, actin monomers and PSTPIP must be present in the assay but "it cannot be ascertained what other components are required to monitor the ability of PSTPIP to induce actin polymerization." The Examiner emphasized that aspects of the assay described in the specification, such as PSTPIP overexpression, were not recited in the rejected claims.

This rejection is now applicable to new claim 23. Consistent with the Examiner's suggestion, claim 23 specifies assay conditions under which a PSTPIP agonist or antagonist antibody may be identified. In particular, claim 23 recites that binding of the agonist or antagonist antibody stimulates or inhibits the polymerization of actin monomers induced by over-expression of the PSTPIP polypeptide within a cell. Applicants submit that as the present amendment identifies the components necessary to monitor the ability of PSTPIP to induce actin polymerization, this rejection should not be applied to claim 23.

With respect to claim 22, the Examiner further reiterates that "in order to practice the invention as claimed, the integrity of a cell membrane would necessarily have to be disrupted in order to contact PSTPIP with an antibody; and one would not expect PSTPIP to function normally in a disrupted, non-viable cell." In response to Applicants' presentation of methods known in the art for conferring membrane permeability to otherwise impermeable proteins, the Examiner states that "if one were to have to resort to such methods to use the invention as claimed, then clearly applicant would have had to refer to these methods in the specification."

Applicants submit that as the methods of conferring membrane permeability were well known in the art at the time of the invention, as evidenced by the cited publications, a description of such methods in the specification is not necessary in order for one of ordinary skill to practice the claimed invention without undue experimentation. In addition, the Examiner has provided no

evidence to support his position that one would not expect PSTPIP to function normally in disrupted cells.

However, without acquiescing to the Examiner's position, new claim 23 recites an assay for identifying a cell permeable agonist or antagonist antibody as suggested by the Examiner. As a cell permeable antibody would not require disruption of the cell membrane, Applicants submit that this rejection should not be applied to new claim 23.

Further, the Examiner has found that "the phrase "followed by wash" in claims 15 and 22 is indefinite because it cannot be determined how many washes are to be performed or for what length of time washes are to be performed." The Examiner also notes that as the wash conditions recited are only "stringent" and not "highly stringent," numerous unrelated polynucleotides will hybridize. This rejection is now also applicable to new claim 23.

Applicants respectfully submit that the stringent conditions recited in the claims are standard stringent hybridization conditions that were well known in the art at the time of the present invention. The determination of the length and frequency of washes necessary to achieve a desired level of non-specific hybridization was well within the capabilities of one of ordinary skill in the art at the time of the invention and would not require undue experimentation. While some experimentation may be necessary to reduce the background to the desired level, this does not constitute undue experimentation.

With regard to the Examiner's concern that stringent hybridization conditions will identify numerous unrelated polynucleotides, Applicants submit that the stringent hybridization conditions are chosen to limit the number of unrelated polynucleotides identified, not to eliminate them. Stringent conditions are specifically chosen when, as here, it is desired to identify related proteins and not simply to identify the presence of an exact polynucleotide sequence in a sample. While such an approach may identify some unrelated proteins, the amount of experimentation necessary to eliminate the unrelated proteins is not undue or excessive. Further, Applicants submit that the polypeptides of the claims are not defined simply by the ability of the nucleic acids that encode them to hybridize to SEQ ID NO: 2 under stringent conditions. Rather, they must also retain the ability to bind to a specifically defined protein tyrosine phosphatase. In view of the ability of one of ordinary skill in the art to limit background

with the claimed stringent conditions and the functional screen for identifying variants, undue experimentation would not be required to practice the claimed invention.

In addition, as discussed above, the claims in the present application cover the same scope of variants as those covered by the issued claims in U.S. Patent No. 6,111,073 for PSTPIP polypeptides. Indeed, both issued independent claims in the '073 patent recite the identical "followed by wash" language and are supported by an identical specification. In view of the issued claims, it would be prejudicial to Applicants to maintain this rejection.

The Examiner goes on to note that "as the claims are written the scope of the invention encompasses an antibody that binds to a PSTPIP polypeptide variant that retains the ability to bind a protein tyrosine phosphatase and which does not have the ability to induce the polymerization of actin monomers." The Examiner concludes that since the specification does not teach how to use a PSTPIP variant that does not have the ability to induce actin polymerization, "one of skill in the art cannot use the invention to the full breadth of the claims without undue experimentation."

Claim 15 and new claim 23 now recite that the PSTPIP variants retain the ability to induce actin polymerization. Applicants submit that as the claims no longer cover PSTPIP variants that are incapable of stimulating actin polymerization, the claimed genus of PSTPIP variants is disclosed in the specification and this rejection should be withdrawn.

Claim Rejections Under 35 U.S.C. §102(b)

The rejection of claims 15 through 18 under 35 U.S.C. §102(b) as being anticipated by Sodhi et al. (*Biochemistry and Molecular Biology International*, 35:559-565 (1995)) and Frackleton et al. (*Journal of Biological Chemistry* 259:7909-7915 (1984)) has been maintained. The Examiner states that the anti-phosphotyrosine antibodies disclosed in these references would specifically bind a phosphorylated tyrosine residue in the polypeptide of the claims.

Claim 15, from which claims 16-18 depend, has been amended in a manner consistent with the Examiner's suggestion to recite an antibody that "binds specifically" to a PSTPIP polypeptide. As the Examiner makes clear, the antibodies taught by Sodhi et al. and Frackleton et al. specifically bind to phosphorylated tyrosine residues in any protein. Applicants submit that

they do not bind specifically to the claimed PSTPIP polypeptides and therefore, that this rejection should be withdrawn.

The Examiner indicated that the phrase "polypeptide epitope" is not supported by the specification and introduces new matter. Without acquiescing in the Examiner's position, claim 15 has been amended to delete the phrase "polypeptide epitope." Additionally, this phrase is not found in new claim 23.

Claims 15 and 17 were also rejected under 35 U.S.C. §102(b) as being anticipated by Su et al. (*Biotechniques* 13:756-762 (1992)). Su et al. describe the use of anti-FLAG antibodies for the immunoaffinity purification of recombinant TNF-α containing FLAG peptide. The Examiner stated that the prior art antibody of Su et al. "clearly anticipates the claim, because the prior art antibody is capable of specific binding to a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1."

As discussed above, Applicants have amended claim 15 to recite an antibody that "binds specifically" to a PSTPIP polypeptide. Applicants submit that as an anti-FLAG antibody would bind any polypeptide containing a FLAG-peptide, it would not bind specifically to a PSTPIP polypeptide.

Because the antibody disclosed in the Su et al. reference does not anticipate claims 15 and 17, Applicants respectfully submit that this rejection is no longer appropriate.

The Examiner has also maintained the rejection of claim 15 as being anticipated by Parthun et al. (Journal of Biological Chemistry 265:209-213 (1990)). Parthun et al. teach the use of an antibody directed against Gal4 protein and the Examiner states that "the polynucleotide sequence in SEQ ID NO: 2 does encode at least a portion of GAL4 protein." However, the Examiner appears to recognize that the Gal4 sequence is not included within the polynucleotide sequence that encodes SEQ ID NO: 1.

Again, claim 15 has been amended to recite an antibody that "binds specifically" to a PSTPIP polypeptide. An antibody that recognizes the Gal4 sequence would not bind specifically to a PSTPIP polypeptide. As a result, Applicants submit that claim 15 is not anticipated by the Parthun et al. reference and submit that this rejection should not be maintained.

Claim Rejections Under 35 U.S.C. §103(a)

The rejection of claims 15 and 16 under 35 U.S.C. §103(a) as being unpatentable over Bennett et al. or Geneseq Data Bank search result 3, in view of U.S. Patent No. 5,001,225-A has been maintained. Like the rejection over Parthun et al., this rejection is based on the disclosure of anti-Gal4 antibodies and the identification of residues within SEQ ID NO: 2 that allegedly encode at least a portion of the Gal4 protein. As discussed above, an antibody that recognizes the Gal4 sequence would not bind specifically to a PSTPIP polypeptide. Thus, in view of the amended language of claim 15, this rejection should not be maintained.

Conclusion

For the reasons presented above, Applicants respectfully submit that all pending claims are in condition for allowance, and an early action to that effect is respectfully solicited. If any issues remain or require further clarification, the Examiner is respectfully requested to call Applicants' counsel at the number listed below in order to resolve such issues promptly.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 6, 2001

By: _____

Ginger Dreger
Registration No. 33,055
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(415) 954-4114

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The paragraph beginning at page 1, line 4 has been amended as follows:

--This application claims priority under 35 USC §119(e) to U.S. Provisional Application No. 60/104,589, filed February 7, 1997 and under 35 USC §120 to U.S. Application No. 08/938,830, filed September 29, 1997~~, U.S. Application No. 08/798,419 filed February 7, 1997~~ and PCT Application 98/01774 filed January 30, 1998.--

Claim 22 has been cancelled and new claim 23 has been added.

Claim 15 has been amended as follows:

--15. (Three times amended) An antibody that binds specifically~~capable of specific binding~~ to ~~a polypeptide epitope of~~ a PST phosphatase interacting protein (PSTPIP) polypeptide selected from the group consisting of

(i) a polypeptide comprising the amino acid sequence of the PSTPIP polypeptide shown in Fig. 1A (SEQ ID NO: 1); and

(ii) a polypeptide encoded by nucleic acid which hybridizes under stringent conditions to the complement of nucleic acid residues 682 to 1926 of SEQ ID NO: 2, said stringent conditions comprising hybridization in a solution containing 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6-8), 0.1% sodium pyrophosphate, 5x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% sodium dodecyl sulfate (SDS) and 10% dextran sulfate at 42°C followed by wash at 42°C in 0.2 x SSC and 0.1% SDS, and which has both ~~said polypeptide retaining~~ the ability to stimulate actin polymerization and the ability to bind to a protein tyrosine phosphatase which (a) possesses a non-catalytic domain comprising a region rich in proline, serine and threonine residues and a C-terminal 20 amino acid segment which is rich in proline residues, and (b) defines at least one SH3 binding domain~~ wherein said stringent conditions are hybridization in a solution containing 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6-8), 0.1% sodium pyrophosphate, 5x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% sodium dodecyl sulfate (SDS) and 10% dextran sulfate at 42°C followed by wash at 42°C in 0.2 x SSC and 0.1% SDS~~.--

TYROSINE PHOSPHORYLATED CLEAVAGE FURROW-ASSOCIATED PROTEINS (PSTPIPs)

ABSTRACT OF THE DISCLOSURE

This invention concerns new PSTPIP polypeptides which are bound by and dephosphorylated by the PEST family of protein tyrosine phosphatases. The invention specifically concerns native murine PSTPIP polypeptides and their homologues in other mammals, and their functional derivatives. The invention further relates to nucleic acids encoding these proteins, vectors containing and capable of expressing such nucleic acid, and recombinant host cells transformed with such nucleic acid. Methods for inducing the polymerization of actin monomers in eukaryotic cells and assays for identifying antagonists and agonists of the PSTPIP polypeptides of the present invention are also provided.

OK TO ENTER SR 11/12/01